



## Protocol and description of literature searches for the risk-benefit assessment of fish in the Norwegian diet

**From the Scientific Committee of the Norwegian Scientific Committee for Food and Environment**

From the Norwegian Scientific Committee for Food and Environment (VKM) 2020

Protocol and description of literature searches for the risk-benefit assessment of fish in the Norwegian diet

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# **Protocol and description of literature searches for the risk-benefit assessment of fish in the Norwegian diet**

## **Preparation of the opinion**

A project group prepared this protocol for the risk-benefit assessment of fish in the Norwegian diet. The project group consisted of one VKM member from the Steering Committee/the Panel on Contaminants, three VKM members from the Panel on Nutrition, Dietetic Products, Novel Food and Allergy, two VKM members of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics, seven external experts, and four employees of the VKM secretariat. The Steering Committee of the Norwegian Scientific Committee for Food and Environment evaluated and approved the protocol drafted by the project group.

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## **Competence of VKM experts**

Persons working for VKM, either as appointed members of the Committee or as external experts, do this by virtue of their scientific expertise, not as representatives for their employers or third party interests. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

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# Abbreviations and acronyms

AMSTAR	A MeaSurement Tool to Assess systematic Reviews
BHT	Butylhydroxytoluene
bw	Body weight
CHD	Coronary heart disease
DALY	Disability-adjusted life year
DHA	Docosahexaenoic acid
DRV	Dietary reference values
EFSA	European Food Safety Authority
EPA	Eicosapentaenoic acid
HBGV	Health-based guidance value
IMR	Institute of Marine Research
IOM	Institute of Medicine
KBS	Nutritional calculation software (KostBeregningsSystem)
LOD	Limit of detection
LOQ	Limit of quantification
MeHg	Methyl mercury
ML	maximum level
NAM	National Academy of Medicine (USA)
NDH	Norwegian Directorate of Health
NFSA	Norwegian Food Safety Authority
NIPH	Norwegian Institute of Public Health
NIFES	National Institute of Nutrition and Seafood Research

NNR	Nordic Nutrition Recommendations
OHAT	Office of Health Assessment and Translation
OIM	Observed Individual Means
PCB	Polychlorinated biphenyl
PFAS	Perfluoroalkyl substances
PreventADALL	Preventing Atopic Dermatitis and ALLergies
QALY	Quality-adjusted life year
RA	Risk assessment
RBA	Risk-benefit assessment
RBQ	Risk-benefit question
TEF	Toxic equivalency factor
ToR	Terms of reference
VKM	Norwegian Scientific Committee for Food and Environment (Vitenskapskomiteen for mat og miljø)
WoE	Weight of evidence
WCRF	World Cancer Research Fund

# 1 The request from the Norwegian Food Safety Authority

## 1.1 Background

Fish contains nutrients that are positive for our health. At the same time, it contains varying levels of undesirable substances that can have a negative effect on health. Undesirable substances can be found in different levels in most types of food. In a risk-benefit assessment, both the nutrients and the undesirable substances are assessed and it is evaluated whether it in total gives a more positive effect to eat certain foodstuff than not, and possibly how much one should eat to achieve optimal use of the positive health effects.

A risk-benefit assessment of fish has been conducted two times previously by the Norwegian Scientific Committee for Food and Environment (VKM). The reports were published in 2006 and 2014. In 2006, VKM pointed out that consumption of fish had positive effects on public health, especially because of the content of polyunsaturated fatty acids and vitamin D (VKM, 2006). VKM also found that mainly mercury, dioxins and dioxin-like-PCBs posed a potential risk when consuming fish in Norway. In 2014, VKM concluded that the health benefits by eating fish clearly outweighed the risk of negative health effects from the exposure to undesirable substances from fish (VKM, 2014). According to the committee, it was well documented that fish protects against cardiovascular disease. Further on, in the assessment VKM concluded that fish contributes to a positive development of the neural system in the foetus and in breastfed infants, and that they can miss out on these effects if the mother does not eat enough fish (i.e. less than one dinner portion per week).

The role of the Norwegian Food Safety Authority (NFSA) is to warn the population against foods that can contain too high levels of substances that can give negative health effects. In addition, the NFSA contributes in the work to develop regulations and maximum levels (MLs) for contaminants in foodstuffs, which also is a means to protect the population. The Norwegian Directorate of Health (NDH) gives advice on diet that describes what one should eat to get the best possible health effects from our diet.

After 2014, several new data relevant for a risk-benefit assessment of fish has become available. The Institute of Marine Research (IMR) has on commission from NFSA and others collected occurrence data for undesirable substances and nutrients in fish species that we did not have sufficient data on in earlier assessments. The Department of Nutrition at the University of Oslo has, in collaboration with the Norwegian Institute of Public Health (NIPH), NDH and NFSA, completed diet studies of children and adolescents (4-, 9-, and 13-year-olds) in 2015-2016 (Hansen et al., 2016). In addition to more data available, the general knowledge has also increased. Several tolerable weekly intakes (TWIs) for undesirable

substances have been revised by the European Food Safety Authority (EFSA). The most important ones were published in 2018 and are summarised below:

In November 2018, EFSA published a new risk assessment of the substance group dioxins and dioxin-like-PCBs in food and feed (EFSA et al., 2018b). In this assessment, EFSA concluded that the tolerable weekly intake level for this substance group should be lowered from 14 to 2 pg/kg body weight per week. The new tolerable intake protects against reduced sperm concentration. In the assessment, EFSA also suggested that the WHO-TEF-value (which describes the relative toxicity of the substances in the group compared with the most toxic substance of dioxins, 2,3,7,8-TCDD) for PCB-126 probably is too high and should be revised. A revision will probably take at least one year. It is therefore important that the risk-benefit assessment in fish can adjust to possible new WHO-TEF-values.

In December 2018, EFSA published a risk assessment of the perfluoroalkylated substances, PFOS and PFOA, in food (EFSA et al., 2018a). Also in this assessment EFSA concluded that the health-based guidance values should be lowered for both substances. For PFOS, the TWI level was lowered from 150 to 13 ng/kg body weight per week. The new TWI value protects against risk of increased cholesterol in adults, and reduced effect of vaccines in children. For PFOA, the TWI was reduced from 1500 to 6 ng/kg body weight per week. The new tolerable intake protects against increased cholesterol. The conclusions in the assessment are provisional until a second assessment of other PFAS is ready. It is therefore important that the risk-benefit assessment of fish in the Norwegian diet can be adjusted to possible changes in the PFAS TWI when the second assessment is published.

With regard to the new knowledge available, NFSA requested a new risk-benefit assessment of fish in the Norwegian diet.

## 1.2 Terms of reference (ToR)

The Norwegian Food Safety Authority (NFSA) asked the Norwegian Scientific Committee for Food and Environment (VKM) to conduct a risk-benefit assessment for fish consumption in the Norwegian diet. In the assignment, they asked VKM to answer the following questions:

Which health consequences will it have for the Norwegian population if they:

- Continue with the same consumption levels as of today
- Increase the consumption of fish to match the recommendations given by the Norwegian Directorate of Health (NDH)<sup>1</sup>

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<sup>1</sup> "Eat fish for dinner two to three times a week. Also use fish as spread on bread. The advice equals 300-450 grams of fish filets during the week. At least 200 grams should be fatty fish like salmon,

- Reduce the consumption of fish and replace parts or all of it with other foods in the diet (this is however not covered in this protocol, See 1.3 “Scope of the protocol” below)

VKM will decide which substances and scenarios that should be included to conduct a relevant risk-benefit assessment of fish consumption. The decisions will need to be justified in the assessment. The assessment of dioxins and dioxin-like-PCBs should be done in a manner that allows for later adjustments if/when the toxic equivalency factor (TEF) values are revised. Perfluoroalkylated substances (PFAS) should also be assessed in a manner that makes it possible to adjust the assessment to new health-based guidance values (tolerable intakes<sup>2</sup>).

Data gaps and insufficient data (e.g. too high limit of quantification, LOQ) should be made visible in the assessment; this information will be useful for planning future data collection.

### **1.3 Scope of the protocol**

This protocol will describe how the project group intends to answer the two first questions of the ToR. How the project group intends to answer the 3rd question of the ToR, related to substitution of fish with other foods in the diet, will *not* be covered in this protocol. The reason for this limitation is merely the timeframe of the project. The project group has prioritised to start with the first part of the ToR.

The protocol has been developed with the aim of being open and transparent about the risk-benefit assessment (RBA) process, the choices that are made, and the limitations and restrictions that are set.

This is done by defining the strategy for data collection (i.e. which data to use for the assessment, and how to identify and select them), and presenting the criteria that will be applied for inclusion or exclusion of compounds and health effects in the assessment. In addition, those compounds that were given in the mandate, or for other reasons already decided to be included, are listed here, together with the reasoning for their inclusion.

Due to the limited time available, the project group has already performed a literature search for fish consumption and a defined set of health outcomes. How the search has been

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trout, mackerel or herring. Six portions of fish used as bread spread equals approximately one portion of dinner.” Matportalen.no (downloaded 09.04.19).

<sup>2</sup> Tolerable intake (which is a health-based guidance value) describes the maximum intake of substances in food, such as nutrients or contaminants, that can be consumed daily or weekly over a lifetime without risking adverse health effects.

performed, as well as how we have identified and chosen health outcomes, are thoroughly described in this protocol.

How we intend to appraise the relevant evidence, and to analyse and integrate the evidence in order to draw conclusions that will form the basis for the Scientific Opinion, are described in brief.

# 2 Problem formulation

## 2.1 Objectives

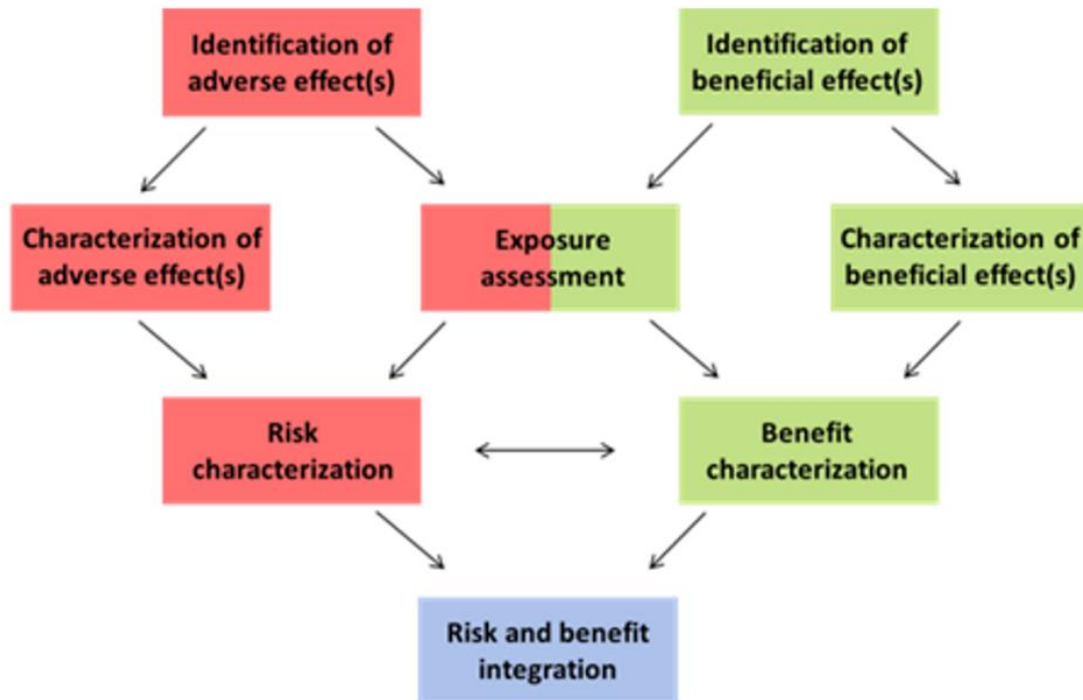
The overall aim is to weigh the risks and benefits associated with fish consumption. See Figure 2.1-1 for a schematic view of the process. The sub-objectives will be to:

1. Identify and characterise adverse and beneficial health effects related to eating fish, i.e;
  - a. Identify relevant adverse and beneficial health effects associated with consumption of fish as such
    - i. Evaluate the quality of scientific evidence for the associations through a systematic literature search, a quality assessment, and a weight of evidence (WoE) approach
    - ii. Characterise the adverse and beneficial effects and, if possible, describe dose-response relationships
  - b. Identify relevant contaminants where fish is an important contributor to the total dietary exposure
    - i. Identify relevant adverse health effects associated with exposure to the relevant contaminants from fish and fish products
    - ii. Evaluate the quality of scientific evidence for the associations
    - iii. Characterise the adverse effects and, if possible, describe dose-response relationships
  - c. Identify relevant micro- and macronutrients where fish is an important contributor to the total dietary exposure
    - i. Identify relevant beneficial, and possible adverse, health effects associated with intake of the nutrients from fish and fish products
    - ii. Evaluate the quality of scientific evidence for the associations
    - iii. Characterise the beneficial effects and, if possible, describe dose-response relationships
2. Calculate fish consumption and exposure to contaminants and nutrients identified in sub-objective 1.b and 1.c, using the various scenarios;
  - a. The Norwegian population continue with the same fish consumption levels as of today
  - b. The Norwegian population increase the consumption of fish to match the recommendations given by the Norwegian Directorate of Health (NDH)<sup>3</sup>
3. Perform a risk characterisation
4. Perform a benefit characterisation
5. Perform a risk-benefit comparison/integration

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<sup>3</sup> "Eat fish for dinner two to three times a week. Use also fish as a bread spread. The advice equals 300-450 grams of fish filets each week. A minimum of 200 grams should be fatty fish like salmon, trout, mackerel or herring. Six portions of fish used as bread spread equals approximately one dinner portion". Matportalen.no (downloaded 09.04.19).

6. Identify and describe uncertainties and knowledge gaps



**Figure 2.1-1:** Schematic description of the steps in the risk-benefit assessment.

## 2.2 Target population

The target population is the general Norwegian population, both sexes, including children, adolescents and adults.

## 2.3 Limitations

The risk-benefit assessment of fish will be based on the intake estimates of fish as such, including all intake of fish, from fish filet and fish products (like fish cakes, fish fingers, fish gratin etc.), and in addition the exposures of selected contaminants and nutrients found in



fish. The assessment will *not* cover the consumption of other seafood<sup>4</sup>, fish oils or other marine oils.

Levels of both nutrients and contaminants in fish vary between fat and lean fish and between species, and there may be geographical differences. Geographical differences will not be specifically addressed<sup>5</sup>, whereas species of fish, and whether the fish is of freshwater or marine, as well as of wild or farmed origin, will be taken into consideration when relevant. Foodborne pathogens will not be covered in the risk assessment.

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<sup>4</sup> Seafood is not included in the recommendation for fish consumption from the Norwegian Directorate of Health.

<sup>5</sup> NFSA provide specific warnings for fish from areas with high levels of contaminants.

# 3 Identification and characterisation of health effects

To make a risk-benefit assessment of fish in the Norwegian diet, the adverse and beneficial health effects related to eating fish, and relevant nutrients and contaminants present in fish (see above), need to be identified and characterised.

The following sections describe how VKM plans to identify and characterise health effects associated with fish consumption, to select nutrients and contaminants, and to identify health effects from the selected nutrients and contaminants.

## **3.1 Identification and characterisation of health effects associated with fish consumption**

Fish consumption is linked to a variety of health outcomes. The possible health outcomes from fish consumption to be included in this RBA have already been identified in a separate step as described below (see 3.1.1), before a systematic literature search for associations and effect estimates was performed. An evaluation of the quality of the scientific evidence for associations and effect estimates will be performed using a WoE approach. The included health effects will be characterised, and if possible, dose-response relationships will be identified.

In the following, the process is described in more detail.

### **3.1.1 Identification of relevant health outcomes to include in the literature search**

The project group have identified relevant health outcomes to include in the search. The project group initially discussed if it would be possible to perform an open search for all health outcomes and fish intake, but concluded that this would be too comprehensive and the outcome from an open literature search would be overwhelming. The health outcomes identified are:

- The most widespread non-communicable diseases in the Norwegian population
- Health outcomes with a well-established association to fish intake
- Health outcomes with a well-established association to compounds, both contaminants and nutrients, found in fish

World Cancer Research Fund (WCRF) published a high quality updated report on fish consumption and all type of cancers in 2018 (see Appendix 1), and the project group

decided to use information from this report in the RBA, and not include cancer as an outcome in the literature search (WCRF/AICR, 2018).

Health outcomes with a well-established association to fish were identified from published systematic reviews and meta-analyses, as well as previously published national and international risk-benefit assessments of fish (from VKM and EFSA).

Health outcomes associated with contaminants in fish were identified from relevant national and international science-based assessments that had performed systematic literature searches (risk assessments from EFSA). Health outcomes associated with nutrients were identified from published systematic reviews and meta-analyses. The inclusion and exclusion of compounds and related health outcomes are further described in Chapter 3.2 and 3.3.

To check if there were any updated systematic literature reviews available that were thorough enough to replace our own search for fish consumption and the chosen outcomes, a search for 'fish consumption' and 'systematic reviews' or 'meta-analyses' was performed in Medline and Embase. This search was performed on November 25, 2019. It was limited in time to the years 2015-2019. This search for reviews and meta-analyses resulted in 246 hits. None of these met the eligibility criteria, and hence a new search was performed as planned.

### **3.1.2 Systematic literature search and screening**

Librarians at the NIPH performed a first literature search on November 25, 2019. The search strategy is included in Appendix II. This search was performed in the Medline, Embase, and PsychInfo databases, and resulted in 21 857 unique hits. These were screened, as described below, during the first half of 2020. Updated and/or additional searches may be performed later if needed, and papers may also be included via "snowballing"/citation chasing.

To identify search terms and text words for the relevant health outcomes, VKM used the project group's expertise, and when needed, counselled other experts.

A systematic approach is used for the selection of papers/studies from the literature search. Screening of titles and abstracts were performed in a pairwise blinded manner using Rayyan, a web application for systematic reviews (Ouzzani et al., 2016). The screening was performed against pre-defined inclusion/exclusion criteria. These criteria are given in Table 3.1.2-1 below.

After the first round of screening, the blinding was removed, and the reviewers discussed conflicting decisions. If the two reviewers were unable to reach an agreement, the paper in question was included. If two articles were published from the same cohort data, but in different follow-up durations, the article with the longest follow-up study were chosen.

The potentially relevant papers selected via the screening procedure based on title and abstract was then reviewed in full text. This was done in a similar, pairwise blinded manner, using Rayyan, and based on the same inclusion and exclusion criteria.

The two rounds of screening resulted in 344 full text papers. These will be quality assessed as described below (3.1.3 Quality assessment).

**Table 3.1.2-1.** Inclusion/exclusion criteria for literature from the systematic search related to fish intake and health outcomes.

<b>Criteria for inclusion</b>	<ul style="list-style-type: none"> <li>• Studies investigating fish intake in relation to one or more health outcomes that was included in the systematic search</li> <li>• Study designs:             <ul style="list-style-type: none"> <li>○ Longitudinal observational studies, such as: Cohort studies, Case-cohort studies, Nested case-control studies, Case-control studies</li> <li>○ Experimental studies, such as: Randomised Controlled Trials (RCTs), Controlled Clinical Trials (CCTs), Controlled Before-and-After studies (CBAs)</li> </ul> </li> <li>• Population: general population, all age groups. Persons with the following conditions are considered part of the general population and will be included:             <ul style="list-style-type: none"> <li>○ Diabetes type 2</li> <li>○ Obesity</li> <li>○ Musculoskeletal disorders</li> </ul> </li> <li>• Publication type: original papers</li> <li>• Other: fish intake needs to be measured at individual level, effect estimates must be given. Studies on secondary prevention should be included</li> </ul>
<b>Criteria for exclusion</b>	<ul style="list-style-type: none"> <li>• Studies investigating fish intake without any relation to the specific health outcomes included in the search</li> <li>• Studies investigating exposure to supplements (omega 3/fish oil/vitamin D)</li> <li>• Dietary pattern-studies</li> <li>• Publication types:             <ul style="list-style-type: none"> <li>○ reviews</li> <li>○ case histories</li> <li>○ letters to editors</li> <li>○ book chapters</li> <li>○ posters</li> <li>○ abstracts</li> </ul> </li> <li>• Population: specific patient groups (see inclusion criteria for exceptions)</li> <li>• Study designs:             <ul style="list-style-type: none"> <li>○ Cross-sectional studies</li> <li>○ Animal studies</li> <li>○ <i>In vitro</i> studies</li> </ul> </li> </ul>

### **3.1.3 Quality assessment**

All the included full text papers/studies will be graded in a three-category rating system considering internal validity. The rating system will be based on an existing, well recognised tool, i.e. either the tool developed for Nordic Nutrition Recommendations (NNR) or the OHAT tool (Nordiska ministerrådet, 2014; NTP, 2015). The chosen tool will be adjusted, optimised and fitted for our purpose.

The review of the full text papers and the methodological quality assessment will be conducted independently by two reviewers. Disagreement on the final rating of a paper will be resolved by consensus. If necessary, a third reviewer will be included for decision.

Only papers graded in one of the two upper categories in the quality assessment will be included in the further process. Papers graded in the lowest category will be excluded from this RBA.

### **3.1.4 Data extraction**

For the papers that pass the quality assessment, a systematic data extraction will be done.

The exact parameters to be extracted will be agreed by the project group in connection with the data extraction. Extracted data will typically include several aspects related to

- i) study characteristics (e.g. country, type of study, number of cases and controls or number of cohorts, year study ended, etc.)
- ii) study population (e.g. ethnicity, gender and age composition, proportion response rate/loss-to-follow-up, etc.)
- iii) exposure (see also chapter 4 below for more details on exposure assessment)
- iv) outcome (e.g. determination of outcome – self-report, registry, medical records, mean/median, covariates adjusted, precision of the effect estimate, etc.)

### **3.1.5 Weight of Evidence (WoE) assessment**

After the quality assessment and the extraction of data, an overall assessment of the weight of evidence for the associations between fish intake and health effects will be performed.

The weighing of the evidence will follow either the guidelines described by WCRF (WCRF/AICR, 2018) or the OHAT guideline (NTP, 2019). The chosen WoE-process will be adjusted, optimised and fitted for our purpose.

The overall evidence grading levels following the WCRF-protocol are summarised in: 1) convincing (strong evidence), 2) probable (strong evidence), 3) limited - suggestive, 4) limited - no conclusion, or 5) substantial effect on risk unlikely (strong evidence). This system, and how it was used for cancer, is shown in Appendix I. The equivalent overall grading following OHAT is 1) high level of evidence, 2) moderate level of evidence, 3) low level of evidence, 4) inadequate evidence, or 5) evidence of no health effect. For a description of the OHAT tool, see NTP, 2019.

Only effects for which the total body of evidence (across studies) is rated in one of the first two categories will be included in a refined RBA. VKM will attempt to establish dose-response curves for these effects, see Chapter 6 for further description of the process.

### 3.1.6 Characterisation of the adverse and beneficial health effects

Dose-response relationships for the included adverse and beneficial health effects from fish consumption will be derived, when possible. If dose-response relationships cannot be derived, reference points for toxicity or nutritional sufficiency will be described.

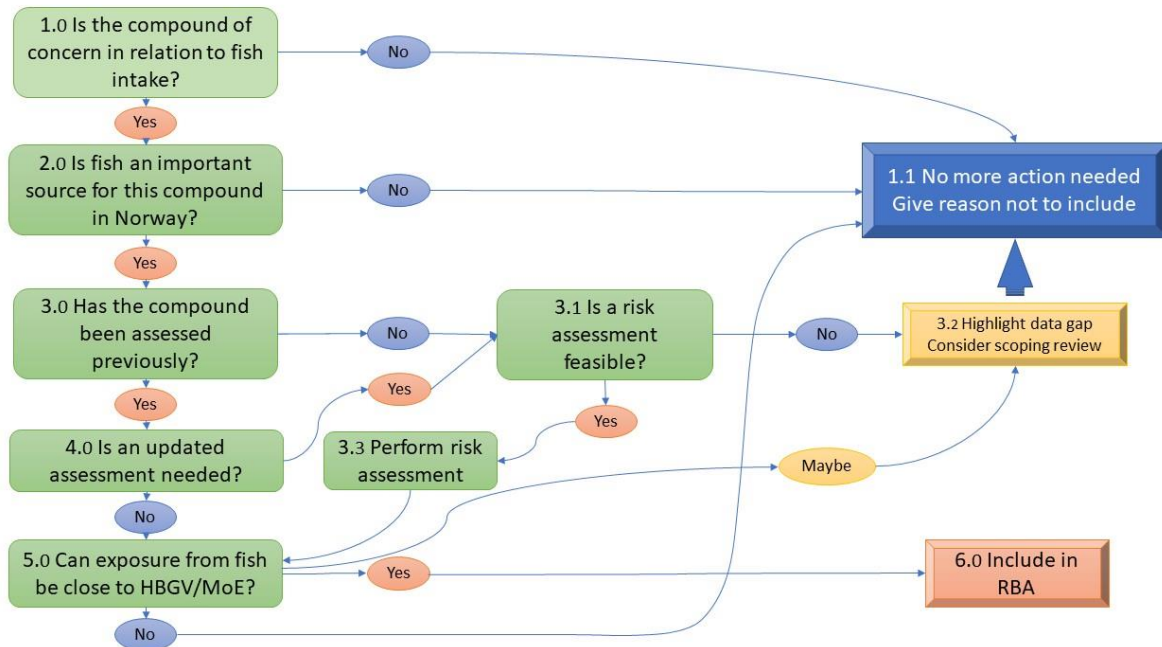
## 3.2 Identification of relevant contaminants

The project group has defined general inclusion/exclusion criteria of contaminants relevant for the RBA. These criteria are given in Table 3.2-1. A list of the compounds that will be considered for inclusion can be found in Appendix III. This is not an exhaustive list, and more compounds may be added and considered for inclusion later.

**Table 3.2-1** Criteria for inclusion or exclusion of contaminants.

Criteria for inclusion	Criteria for exclusion
<ul style="list-style-type: none"> <li>Fish is an important source for exposure AND</li> <li>Exposure in Norway may be above health-based guidance values as described in previous risk assessments</li> <li>Given in the mandate (see table 3.2-2)</li> </ul>	<ul style="list-style-type: none"> <li>Fish is not an important source for exposure</li> <li>Exposure is clearly below health-based guidance values</li> <li>Insufficient data (hazard and/or exposure) to conclude on risk</li> </ul>

Contaminants will be considered for inclusion, based on a decision process outlined in Figure 3.2-1. The final list of compounds to be included will be presented in the final opinion. All other contaminants that are considered for inclusion, but are excluded, will be listed with a given reasoning for exclusion in the final opinion.



**Figure 3.2-1** Flow chart describing decision process for inclusion or exclusion of candidate contaminants for the risk-benefit assessment (RBA) of fish in the Norwegian diet. HBGV: health-based guidance value, MOE: margin of exposure.

Three contaminants to be included have already been identified. These are listed in Table 3.2-2 with the reasons for inclusion.



**Table 3.2-2** Contaminants that are decided will be included in the assessment, and the reasons for including them. Other contaminants may be added later (see text above, and Appendix III, for details).

<b>Contaminant</b>	<b>Reasons for inclusion</b>	<b>Reference(s)</b>
<b>Dioxins and dl-PCB</b>	<ul style="list-style-type: none"> <li>• Given in the mandate</li> <li>• Fish is an important source of exposure</li> <li>• New health-based guidance values (tolerable intakes) from EFSA, and exposure in Norway may be above the new health-based guidance value (HBGV)</li> </ul>	(EFSA et al., 2018b)
<b>PFAS</b>	<ul style="list-style-type: none"> <li>• Given in the mandate</li> <li>• Fish is an important source of exposure</li> <li>• New health-based guidance values (tolerable intakes) from EFSA, and exposure in Norway may be above the new HBGV</li> </ul>	(EFSA et al., 2018a)
<b>MeHg</b>	<ul style="list-style-type: none"> <li>• Fish is an important source of exposure</li> <li>• Exposure in Norway may be above health-based guidance values as described in previous risk assessments</li> </ul>	(EFSA, 2012; EFSA, 2015; VKM, 2014; VKM et al., 2019)

### **3.2.1 Identification of health effects associated with the included contaminants**

The purpose of the identification of health effects related to the included contaminants was, in step one; to identify relevant search terms and text words for the search strategy for fish consumption (see section 3.1.1). In step two, we want to characterise the effects to include in the RBA, and to identify dose-response relationships where possible.

Table 3.2.1-1 shows criteria for inclusion/exclusion of health effects related to the included contaminants.

**Table 3.2.1-1** Criteria for inclusion or exclusion of health effects for the contaminants.

Criteria for inclusion of health effects	Criteria for exclusion of health effects
<ul style="list-style-type: none"> <li>Health effect considered causal or critical in previous risk assessments</li> <li>Intermediate endpoints are included only if evidence is good and consistent both for association between compound and intermediate endpoint as well as for an association between intermediate endpoint and health outcome</li> </ul>	<ul style="list-style-type: none"> <li>Effect is not likely to occur, or is not described, for doses relevant for fish consumption</li> <li>Intermediate endpoints are excluded if consistent evidence is lacking either for association between compound and intermediate endpoint or for an association between intermediate endpoint and health outcome</li> </ul>

Health effects from contaminants for step one were identified from relevant national and international science-based assessments that had performed systematic literature searches (risk assessments from EFSA). The same approach will be attempted for in step two. Hence, VKM will not perform their own literature searches on health effects from contaminants, unless previous risk assessments are clearly outdated.

### 3.3 Identification of relevant micro- and macronutrients

The project group has defined general inclusion/exclusion criteria for nutrients that may be included in the RBA. These criteria are given in Table 3.3-1. Evidence for beneficial or detrimental health effects will be based on previous risk-benefit assessments, and updated systematic reviews and meta-analyses. The final list of nutrients to be included will be presented in the final opinion. All other nutrients that are considered for inclusion according to the criteria in Table 3.3-1, but are excluded, will be listed with a given reasoning for exclusion in the final opinion.

**Table 3.3-1** Criteria for inclusion or exclusion of nutrients.

Criteria for inclusion	Criteria for exclusion
<ul style="list-style-type: none"> <li>Fish is an important source of exposure AND</li> <li>Good and consistent evidence exists for a beneficial or detrimental health effect</li> </ul>	<ul style="list-style-type: none"> <li>Fish is not an important source of exposure</li> <li>Lack of evidence for health effect and/or exposure</li> </ul>

Two nutrients have already been identified that are to be included. These are listed in Table 3.3-2 with the reasons for inclusion.

**Table 3.3-2** Nutrients that are decided will be included in the assessment, and the reasons for including them. Other nutrients may be added later (see text above for details).

Nutrient	Reasons for inclusion	Reference(s)
<b>DHA/EPA</b>	<ul style="list-style-type: none"> <li>• Fish is one of the most important sources of exposure</li> <li>• Good and consistent evidence exists for several health effects: Coronary heart disease (CHD), preterm birth and birth weight</li> </ul>	(Totland et al., 2012) (Alexander et al., 2017) (Balk et al., 2016) (Wan et al., 2017) (Middleton et al., 2018)
<b>Vitamin D</b>	<ul style="list-style-type: none"> <li>• Fish is one of the most important sources of exposure</li> <li>• Good and consistent evidence exists for several health effects: bone health, mortality</li> </ul>	(Totland et al., 2012) (NNR, 2012) (IOM, 2011) (Yao et al., 2019)

### 3.3.1 Identification of health effects associated with included nutrients

The purpose of identification of health effects related to the included nutrients was, as for the contaminants, in step one; to identify relevant search terms and text words for use in the search strategy for fish consumption (see section 3.1.1). In step two; the project group will characterise the effects, and identify dose-response relationships where possible, to include in the RBA.

Table 3.3.1-1 shows criteria for inclusion/exclusion of health effects related to the included nutrients.

Health effects associated with the selected nutrients are identified from published systematic reviews or meta-analyses. VKM will not perform a systematic search on each nutrient.

For step one, to identify relevant outcomes for use in the search strategy for fish consumption, it was essential to include all potentially important health outcomes. Therefore, both outcomes with less consistent evidence and good and consistent evidence were included in this step.

For step two, to identify health outcomes to include in the RBA, with good and consistent evidence for associations to the relevant nutrients, the project group will search for, and only include, high quality systematic reviews/meta-analysis. For some intermediate endpoints (see Table 3.3.1-1), Clinical Trials (ClinicalTrials.gov) may also be a source of good and consistent evidence. Data from Clinical Trials will be considered when relevant. The quality of the reviews/meta-analysis will be judged using AMSTAR 2 (Shea et al., 2017).

The overall grade of evidence will decide which health effects to include in the present RBA. I.e., only health effects where the overall evidence is graded as convincing or probable/very likely or likely, will be included. For the grading, we will use either the guidelines described by WCRF or the OHAT guideline.

**Table 3.3.1-1** Criteria for inclusion or exclusion of health effects for the included nutrients.

Criteria for inclusion of health effects	Criteria for exclusion of health effects
<ul style="list-style-type: none"> <li>• Evidence for an association between nutrient effect and health outcome is good and consistent</li> <li>• Source of evidence: Systematic reviews or meta-analyses published in one of the following (or equivalent): Cochrane Database, NNR, IOM/NAM; OR assessment published by EFSA or VKM</li> <li>• Intermediate endpoints are included only if evidence is good and consistent both for association between compound and intermediate endpoint as well as for an association between intermediate endpoint and health outcome</li> </ul>	<ul style="list-style-type: none"> <li>• Evidence for an association/effect is limited or inconsistent</li> <li>• Effect is not likely to occur, or is not described, for doses relevant for fish consumption</li> <li>• Intermediate endpoints are excluded if consistent evidence is lacking either for association between compound and intermediate endpoint or for an association between intermediate endpoint and health outcome</li> </ul>

# 4 Exposure assessment

Occurrence data and consumption data are needed to calculate the exposure, both for the risks and the benefits.

The exposure estimations will be performed for chronic exposure only. For the occurrence, mean values will be used (more details are given below in Table 4.1-1). The consumption estimates will be made using the Observed Individual Means method (OIM; semi-deterministic), and custom-made scripts in R (probabilistic). Probabilistic estimates rely on distributions as inputs, in place of single values, for key parameters. This results in a distribution of possible exposure estimates and gives the ability to characterise variability and uncertainty.

Person-specific body weights will be used where possible; otherwise Norwegian age- and gender-specific body weights will be used.

## 4.1 Occurrence data

**Table 4.1-1.** Occurrence data that will be used in the exposure calculations.

<b>Compound(s)</b>	<b>Occurrence data available</b>
<b>Dioxins and dioxin-like PCBs</b>	Data on fish species analysed by the Institute of Marine Research (IMR)
<b>PFAS</b>	Data on sushi analysed by the National Institute of Nutrition and Seafood Research (NIFES, now IMR)
<b>MeHg</b>	Data available in the EFSA (2018) assessment «Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food» (EFSA et al., 2018b)  Data available in the EFSA (2018) assessment «Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanic acid in food» (EFSA et al., 2018a).  If newer data are made available from coming EFSA opinions in the timeframe of this opinion, these will be taken into consideration.
<b>Fatty acids (DHA/EPA)</b>	The KBS (nutritional calculation software) database contain values for fatty acids and vitamin D.
<b>Vitamin D</b>	

The KBS database contains nutrient values for DHA/EPA and vitamin D. Data on fatty acids were updated in 2014 and 2018.

Norwegian occurrence data for foods commonly consumed in Norway will be preferred over pooled European data from EFSA.

Occurrence data of contaminants will be given in lower and upper bound values. Lower bound estimates will be calculated by substituting values below the limit of detection (LOD) or limit of quantification (LOQ) for an analytical method with zero. Upper bound estimates will be calculated by substituting values below the LOQ, or LOD if LOQ is missing, with values set to equal to the LOD or LOQ.

How to handle any lack of occurrence data (e.g., use the most comparable value or set the occurrence to zero) cannot be decided until a complete overview of all available data have been created.

## 4.2 Intake data for exposure calculation

To get the best possible picture of the intake of fish and the whole diet for different population groups, intake data from several types of dietary surveys and studies will be used. The surveys/studies using short-term recall/record methods like 24-hour recalls and 4 days food records give detailed information of food intake over a few days, whereas food frequency methods give less detailed information but for a longer period, like a month or a year.

The Norwegian national food consumption surveys will be used as the basis for the exposure calculations. These include:

- Norkost 3 (Totland et al., 2012)
- Ungkost 3 (Hansen et al., 2016)
- Småbarnkost 3 (data collection 2019, data ready for use 2020)
- Spedkost 3 (data collection 2018/2019, data ready for use 2020)

Norkost 3 and Ungkost 3 are surveys that give detailed information of food intake on an individual level. The dietary methods used are 24-hour recalls and 4-days web record, respectively. For Småbarnkost 3 and Spedkost 3, the dietary assessment method used is food frequency questionnaires.

Data from other surveys and studies, all addressing food frequency, will also be considered used for the exposure calculations or as supporting data for fish intake, and intake of rarely eaten foods:

- Tromsø 7; The seventh survey of the Tromsø Study was carried out in 2015-2016. The questionnaires includes data on diet.
- Hunt4; The HUNT study. The latest data gathering started in 2017. The HUNT Study includes data from questionnaires (including food habits).

- The Norwegian Mother, Father and Child Cohort (MoBa) - the 13-year-olds study, data collected from 2017 and onwards.
- PreventADALL (Preventing Atopic Dermatitis and ALLergies), data were collected in 2014-2016.

# 5 Risk and benefit characterisations

The risk and benefit characterisations will be based on the identified and characterised adverse and beneficial health effects, respectively, as described in Chapter 3, and the estimated exposure from the given scenarios, derived as described in Chapter 4.



# 6 Risk and benefit integration

The weighing of the benefits against the risks will need to take into account the timeframe for the effects to become apparent and their severity/magnitude.

EFSA's guidance on human health risk-benefit assessment of foods (EFSA, 2010) lays out three distinct steps; 1) Initial assessment, 2) Refined assessment and 3) Assessment using a composite metric. The guidance recommends that initial assessment is sufficient when benefits clearly outweigh risks (or vice versa), while step 2, refined assessments, are needed when the risks and benefits do not clearly outweigh each other. Such a refined risk-benefit assessment aims to provide, depending on the availability of data, semi-quantitative or quantitative estimates of risk and benefits at relevant exposures. A semi-quantitative assessment contains comparisons of relevant exposures to health-based guidance values (HBGV; for contaminants), dietary reference values (DRV; for nutrients), and risks and benefits are summarised as probabilities of exceeding or being below, these reference values. Step 3, a more quantitative approach aims to link the exposure to explicit health effects, and report outcomes, where possible, using common metrics, such as incidence or mortality. Information on dose-response relationship, i.e., the relationship between intake of a substance and the size of its health effects, is crucial in order to be able to estimate the size of the health impact associated with a change in diet.

EFSA recommends, if possible, to perform the assessment using a composite metric; i.e., to use weights for various health outcomes (typically Disability-Adjusted Life Year (DALY), Quality-Adjusted Life Year (QALY) or other), to quantify the impacts of scenarios on a common scale of measurement. A quantitative methodology has the advantage that it allows for a comparison of risks and benefits on the same scale, and provides a quantitative expression of the overall health impact of a given change in diet.

From Chapter 1.1 (Background) and 1.2 (Terms of reference) in this protocol, it is clear that the benefits do not clearly outweigh the risks with regard to (more or less) fish consumption, and VKM will perform a refined assessment (Step 2). For health effect/impacts that have sufficient data available to quantify the increase/decrease in incidence and mortality a quantitative assessment will be performed, whereas for compounds for which less data are available, a semi-quantitative approach will be used (i.e. comparison between HBGVs and DRVs).

The transformation of incidence of different health outcomes, including mortality, onto a composite metric (e.g., by using DALY-weights, Step 3) is neither a trivial task, nor an unchallenged scientifically sound approach. The project group will discuss the possibility of performing a full-scale risk-benefit assessment using DALYs, critically evaluate the necessary assumptions for such an approach and consider the potential impact and bias arising from

the availability of underlying data, to decide if this option will be used. This will be done in close dialogue with the NFSA.

## **6.1 Weighing risks and benefits that are assessed by quantitative and qualitative methodology**

If different risks and benefits, to be compared in the RBA, are obtained by different methods (quantitative and qualitative), a comparative diagram/table will be constructed to get a complete overview of the risk-benefit assessment.

# 7 Uncertainty and Data gaps

Factors introducing uncertainty in the various steps of the assessments will be identified and described. VKM will strive to quantify and indicate the impact (direction and preferably also size) of the uncertainties on effect estimates where possible.

Data gaps will be described in a separate chapter.

## 8 References

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# Appendix I

## WCRF Grading of evidence

Lists of criteria for grading of evidence from the WCRF cancer report (2018). The grades shown here are 'convincing', 'probable', 'limited — suggestive', 'limited — no conclusion'.

These will be adjusted to fit our purpose.

### Convincing (strong evidence)

Evidence strong enough to support a judgement of a convincing causal (or protective) relationship, which justifies making recommendations designed to reduce risk of cancer. The evidence is robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates. All of the following are generally required:

- Evidence from more than one study type.
- Evidence from at least two independent cohort studies.
- No substantial unexplained heterogeneity within or between study types or in different populations relating to the presence or absence of an association, or direction of effect.
- Good quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error and selection bias.
- Presence of a plausible biological gradient ('dose-response') in the association. Such a gradient needs not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly.
- Strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures can lead to relevant cancer outcomes.

### Probable (strong evidence)

Evidence strong enough to support a judgement of a probable causal (or protective) relationship, which generally justifies recommendations designed to reduce the risk of cancer. All the following criteria are generally required:

- Evidence from at least two independent cohort studies, or at least five case-control studies.
- No substantial unexplained heterogeneity between or within study types in the presence or absence of an association, or direction of effect.
- Good quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error and selection bias.
- Evidence for biological plausibility.

### Limited — suggestive

Evidence that is too limited to permit a probable or convincing causal judgement but is suggestive of a direction of effect. The evidence may be limited in amount or by methodological flaws, but shows a generally consistent direction of effect. This judgement is broad, and includes associations where the evidence falls only slightly below that required to infer a probably causal association through those where the evidence is only marginally strong enough to identify a direction of effect. This judgement is very rarely sufficient to justify recommendations designed to reduce the risk of **cancer**; any exceptions to this require special, explicit justification. All the following criteria are generally required:

- Evidence from at least two independent cohort studies or at least five case-control studies.
- The direction of effect is generally consistent though some unexplained heterogeneity may be present.
- Evidence for biological plausibility.

#### Limited — no conclusion

Evidence is so limited that no firm conclusion can be made. This judgement represents an entry level and is intended to allow any exposure for which there are sufficient data to warrant Panel consideration, but where insufficient evidence exists to permit a more definitive grading. This does not necessarily mean a limited quantity of evidence. A body of evidence for a particular exposure might be graded 'limited — no conclusion' for a number of reasons. The evidence may be limited by the amount of evidence in terms of the number of studies available, by inconsistency of direction of effect, by methodological flaws (for example, lack of adjustment for known confounders), or by any combination of these factors.

When an exposure is graded 'limited — no conclusion', this does not necessarily indicate that the Panel has judged that there is evidence of no relationship. With further good-quality research, any exposure graded in this way might in the future be shown to increase or decrease the risk of **cancer**. Where there is sufficient evidence to give confidence that an exposure is unlikely to have an effect on **cancer** risk, this exposure will be judged 'substantial effect of risk unlikely'

#### Substantial effect on risk unlikely (strong evidence)

Evidence is strong enough to support a judgement that a particular food, nutrient or physical activity exposure is unlikely to have a substantial causal relation **to cancer** outcomes. The evidence should be robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates. All the following criteria are generally required:

- Evidence from more than one study type.
- Evidence from at least two independent cohort studies.
- Summary estimate of effect close to 1.0 for comparison of high versus low exposure categories.
- No substantial unexplained heterogeneity within or between study types or in different populations.



- **Good-quality studies to exclude, with confidence, the possibility that the absence of an observed association results from random or systematic error, including inadequate power, imprecision or error in exposure measurement, inadequate range of exposure, confounding and selection bias.**
- **Absence of a demonstrable biological gradient ('dose-response').**
- **Absence of strong and plausible experimental evidence, from either human studies or relevant animal models, that typical human exposure levels lead to relevant **cancer** outcomes.**

### **Special upgrading factors**

**These are factors that form part of the assessment of the evidence that, when present, can upgrade the judgement reached. An exposure that might be deemed a 'limited-suggestive' causal factor in the absence, for example, of a biological gradient, might be upgraded to 'probable' if one were present. The application of these factors (listed below) requires judgement, and the way in which these judgements affect the final conclusion in the matrix are stated. Factors may include the following:**

- **Presence of a plausible biological gradient ('dose-response') in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly.**
- **A particularly large summary effect size (an odds ratio or relative risk of 2.0 or more, depending on the unit of exposure) after appropriate control for confounders.**
- **Evidence from randomized trials in humans.**
- **Evidence from appropriately controlled experiments demonstrating one or more plausible and specific mechanism actually operating in humans.**
- **Robust and reproducible evidence from experimental studies in appropriate animal models showing that typical human exposures can lead to relevant **cancer** outcomes.**

# Appendix II

## Search strategy for the search on 'fish intake' and 'health outcomes'

**Database:** Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to November 22, 2019>

**Dato:** 25.11.2019

**Antall treff:** 13 379

#	Searches	Results
1	Fishes/	61460
2	("Fishes" or "Fish").tw,kf.	171534
3	exp Trout/ or exp Salmon/ or Flounder/ or Perciformes/ or Gadus Morhua/ or Carps/ or Tuna/ or Perches/ or Esocidae/ or Anguilla/ or Fish products/	47633
4	("Trout?" or "Salmo trutta" or "Oncorhynchus mykiss" or "Salmo mykiss" or "Salmon?" or "salmo salar" or "Oncorhynchus" or "halibut?" or "flounder?" or "European plaice?" or "Hippoglossus hippoglossus" or "Pleuronectes platessa" or "platichthys flesus" or "Mackerel?" or "scomber scombrus" or "Haddock?" or "Melanogrammus aeglefinus" or "Saithe?" or "Pollachius virens" or "Cod?" or "Gadus Morhua" or "Codling?" or "Stockfish*" or "Clipfish*" or "Pollachius pollachius" or "Pollock?" or "Pollack?" or "Carp?" or "cyprinus carpio" or "merluccius merluccius" or "hake?" or "xiphias gladius" or "swordfish*" or "Tuna" or "Katsuwonus pelamis" or "Thunnus thynnus" or "Perch*" or "Perciform*" or "Perca fluviatilis" or "Clupea harengus" or "Herring?" or "Argentina silus" or	169906

	"Salmo silus" or "Greater argentine" or "smelt?" or "Atlantic argentine" or "Wolffish*" or "Seawolf?" or "Anarhichadidae" or "anarhichas lupus" or "Esocidae" or "Esox lucius" or "Pike?" or "Lophius piscatorius" or "Anglerfish*" or "Monkfish*" or "Anguilla anguilla" or "Eel?" or "Conger conger" or "Sardina pilchardus" or "Sardine?" or "pilchard?" or "Anchov*" or "Engraulis encrasicolus" or "Sprattus sprattus" or "European sprat" or "Brosme brosme" or "Merlangius merlangius" or "Whiting" or "fishproduct?").tw,kf.	
5	or/1-4	335346
6	Eating/ or exp Meals/ or Diet/	203519
7	("eat*" or "ate" or "intake?" or "consumption" or "consume?" or "consuming" or "ingestion" or "meal?" or "diet*" or "dine" or "dinner?" or "lunch*" or "breakfast?" or "snack?").tw,kf.	1158373
8	6 or 7	1200355
9	5 and 8	43283
10	Bone density/ or exp Bone Diseases, metabolic/ or exp Fractures, bone/ or Accidental Falls/	280663
11	("Osteoporosis" or "Rickets" or "Osteomalacia" or "vitamin D deficienc*" or (bone adj2 ("disease?" or "density" or "fracture?" or "fragil*" or "broken" or "deminerali#ation?" or "decalciferation?")) or "Accidental Fall*" or (("Slip?" or "trip?") adj2 "fall*")).tw,kf.	147845
12	exp Human development/ or Child Development/ or Motor disorders/ or Psychomotor Disorders/ or exp Psychomotor Performance/ or Cognition/ or	1489510

	<p>Cognitive dysfunction/ or exp Neurocognitive disorders/ or Mental health/ or exp Academic performance/ or exp Child behavior/ or Impulsive Behavior/ or "Inhibition (Psychology)"/ or exp Language disorders/ or Mental disorders/ or Behavioral Symptoms/ or Behavior/ or Anxiety disorders/ or exp "Bipolar and related disorders"/ or Anger/ or Affect/ or Depression/ or Mood disorders/ or Aggression/ or exp Schizophrenia/ or exp Neurodevelopmental Disorders/ or exp Autism spectrum disorder/ or Attention deficit disorder with hyperactivity/ or Attention/ or Learning/ or Reading/ or Mathematics/ or Aptitude tests/ or Language tests/ or Communication/ or Language/ or Language development/ or Child language/ or Literacy/ or Intelligence/ or Executive function/ or Social behavior/ or Social adjustment/ or Emotional intelligence/ or Emotions/ or Temperament/ or exp Amnesia/ or Memory Disorders/ or Dementia/ or Alzheimer disease/ or Memory, Short-Term/ or Memory, Long-term/</p>	
13	<p>((("Child*" or "infant*" or "f?etal" or "prenatal" or "pre natal" or "postnatal" or "post natal" or "human" or "antepartum period?" or "ante partum period?") adj3 "development?") or "inhibition" or ("brain" adj2 ("damage?" or "injur*" or "development?" or "disorder?")) or "psychomotor" or "psycho motor" or "motor" or "sensorimotor" or "sensori motor" or "sensorymotor" or "sensory motor" or "cognition" or "cognitive function?" or "Mental health" or "Disorder? of higher cerebral function?" or ("psychological" adj ("well being" or "wellbeing")) or (("neurocognit*" or "neuro cognit*" or "neurological" or "nervous system" or "nervoussystem" or "cognitive" or "development*" or "mental") adj2 ("dysfunction?" or "function?" or "decline?" or "deterioration?" or "Defici*" or "illness*" or "retardation?" or "disturbance?" or "impairment?" or "disorder?" or "impact?" or "disabilit*" or "deviation?" or "development?")) or "neurodevelopment*" or "neuro development*" or "autis*" or "asperger" or "kanner?" or "ASD" or "attention deficit" or "hyperactiv*" or "ADDH" or "ADHD" or "AD/HD" or "ADD" or "minimal brain dysfunction" or "impulsiveness" or "dyslexia" or "dyslexic?" or "dyscalculia" or "dyscalculic?" or "attention" or "learning" or "reading" or "mathematic?" or "math" or "maths" or ("aptitude" adj1 "test?") or ("Education" or "Educational" or "academic" or "school") adj1 ("Status" or "attainment?" or "achievement?" or "performance?" or "underachievement?" or "under achievement?" or "score?" or "success*" or "failure?")) or "executive function?" or "information processing" or "school</p>	6453705

	<p>readiness" or "school ready" or "Emotion*" or "socialemotional" or "social emotional" or "socioemotional" or "socio emotional" or ("social" adj ("development?" or "behavio?r" or "adjustment?")) or ("intel?ectual" adj2 ("development?" or "deficien*" or "disorder?" or "retardation?" or "disabilit*" or "disturbance?" or "impairment?")) or "Communication" or "language?" or "literacy" or "literacies" or "IQ" or "intel?igence" or "Speech disorder?" or "mutism?" or "aphasia" or "stutter*" or "dysphasia" or "alexia" or "anxiet*" or "depression?" or "depressive" or "mood disorder?" or "schizophrenia" or "schizophrenic" or "aggression" or "behavio?r*" or "affect" or "anger" or "bipolar" or "Temperament?" or "personalit*" or "amnesia" or "dementia" or "Alzheimer?" or "Parkinson?" or "huntington?" or ("memory" adj3 ("disorder?" or "impairment?" or "disturbance?" or "deficianc*" or "disabilit*" or "short term" or "shortterm" or "long term" or "longterm" or "verbal recognition?"))).tw,kf.</p>	
14	<p>exp Cardiovascular diseases/ or Cerebrovascular disorders/ or exp Ischemia/ or exp Stroke/</p>	2351074
15	<p>((("Cardiovascular" or "heart" or "cardiac" or "myocardial" or "myo cardial" or "cerebrovascular" or "vascular" or "coronary" or "cerebral" or "peripheral" or "endothelial") adj ("disease?" or "disorder?" or "failure" or "event?" or "health" or "effect?" or "accident?" or "calcification?" or "risk factor?" or "riskfactor?" or "syndrom?" or "syndrome?" or "revasculari#ation?" or "arter*" or "function?" or "dysfunction?" or "attack?" or "arrest" or "apoplex*" or "insufficienc*" or "injur*" or "insult?" or "scleros#s" or "stenos#s" or "restenos#s")) or "cardioprotect*" or "cardio protect*" or "high cardiovascular risk?" or "CVD" or "infarct*" or "reinfarction?" or "aneurysm?" or "angina" or "artherosclero*" or "arthero sclero*" or "arteriosclero*" or "arterio sclero*" or "isch?emi*" or "nonisch?emi*" or "non isch?emic" or "thrombos#s" or "thrombolism?" or "tachycardia*" or "tachyarrhythmia?" or "arrhythmia?" or (("ventricular" or "arterial") adj ("fibrillation?" or "compliance?" or "stiffness*")) or "sudden cardiac death?" or "stroke?" or "TIA" or ("brain" adj ("h?emorrhage?" or "accident?" or "attack?" or "infarct*" or "insult?"))).tw,kf.</p>	1759689

16	exp Dental Enamel/ or exp Dental Enamel Hypoplasia/ or Tooth Discoloration/	24170
17	((("dental" or "tooth" or "teeth" or "enamel") adj1 ("enamel" or "discolo?ration?" or "malformation?" or "opacit*")) or "hypo?minerali#ation" or ("developmental" adj3 ("dental" or "teeth" or "tooth" or "enamel") adj3 "defect?")).tw,kf.	29565
18	exp Immunity/ or Respiratory Sounds/ or exp Asthma/ or exp Psoriasis/ or exp Eczema/ or Dermatitis/ or exp Arthritis, Rheumatoid/ or Antibodies, antinuclear/ or exp Respiratory Tract Infections/ or exp Multiple sclerosis/ or Lupus Erythematosus, Systemic/ or Scleroderma, Localized/ or Scleroderma, Systemic/	1065950
19	("immunolog*" or "infection resistance" or "immunity" or "autoimmunity" or "auto immunity" or "immunodeficienc*" or "immuno deficienc*" or ("immun*" adj ("system" or "status" or "defense?" or "defence?" or "deficienc*")) or "vaccination response?" or (("upper" or "lower") adj "respiratory tract infection?") or "respiratory Sound?" or "wheez*" or "asthma*" or "psoriasis" or "eczema*" or "dermatiti*" or "rheumatoid arthritis" or (((("sjogren?" or "sicca") adj "syndrome?") or "syndrom?") or "Antinuclear antibod*" or "Multiple scleros#s" or "Systemic lupus erythematosus" or (("Scleroderma" or "scleros#s") adj1 ("localized" or "systemic")))).tw,kf.	1898586
20	Sperm count/ or Semen/ or exp Infertility, Male/ or exp Spermatozoa/ or Sexual maturation/ or Puberty/	119303
21	("Sperm?" or "semen" or "seminal fluid?" or "ejacul*" or "spermatozo*" or "spermatids" or "spermatocytes" or "spermatogonia" or "Oligospermia" or "Oligozoospermia*" or "Oligoasthenoteratozoospermia" or "asthenozoospermia?" or "asthenospermia?" or "criptozoospermia?" or "azoosperm*" or "globozoospermia?" or "teratospermia?" or "teratozoospermia?" or (("man" or "male?" or "men") adj1 "infertil*") or "Sex* matur*" or "Pubert*").tw,kf.	169521

22	Overweight/ or Obesity/ or Obesity, abdominal/ or Obesity, morbid/ or Adiposity/ or Adipocytes/ or Body weight changes/ or Weight gain/ or Pediatric obesity/ or exp Body size/	497001
23	("obesity" or "obesities" or "obese" or "obesitas" or "adipos*" or "fat overload" or "overweight" or "over weight" or "BMI" or "body mass index" or "bodymass index" or "lean body mass" or "lean bodymass" or "fatness" or "adipocyte?" or "lipocyte?" or (("fat" or "lipid") adj cell?) or ("body" adj ("height?" or "size?" or "weight?")) or ("abdominal" adj ("diameter index" or "height")) or "sagittal abdominal diameter?" or "height weight ratio?" or "waist circumference?" or "waist height ratio?" or "waist to height ratio?" or ("weight" adj1 ("change*" or "gain*")) or ("excess*" adj2 ("fat" or "weight"))).tw,kf.	754653
24	Birth weight/ or Pregnancy outcome/ or Premature birth/ or Growth/	117455
25	("growth" or (("premature" or "pre term" or "preterm") adj "birth?") or "SGA" or (("birth" or "gestational" or "neonatal" or "neo natal" or "newborn" or "new born" or "f?etal" or "f?etus" or "baby" or "babies") adj2 ("weight" or "size?")) or (("Pregnancy" or "birth" or "obstetric") adj "outcome?").tw,kf.	1480176
26	("allerg*" or "hypersensitivit*" or "hyper sensitivit*" or "sensiti#ation*" or "atopic?" or "atopy" or "atopies") adj5 "prevention").tw,kf.	2899
27	exp Diabetes mellitus/	412389
28	("diabetes" or "sugar sickness" or "hypoglycemia" or "hypo glycemia" or "hyperglycemia" or "hyper glycemia").tw,kf.	542723
29	exp Goiter/	32486

30	("goiter? " or "goitre?").tw,kf.	20598
31	exp Mortality/	368554
32	("mortalit*" or "death rate?" or "deathrate?").tw,kf.	742658
33	or/10-32	13158760
34	9 and 33	23971
35	Animal/ not (animal/ and human/)	4612090
36	34 not 35	13983
37	limit 36 to (danish or english or french or german or multilingual or norwegian or swedish)	13379



**Database:** Embase 1974 to 2019 November 22

**Dato:** 25.11.2019

**Antall treff:** 15 922

#	Searches	Results
1	Fishes/	83365
2	("Fishes" or "Fish").tw,kw.	208867
3	exp Trout/ or exp Salmon/ or Flounder/ or Perciformes/ or Gadus Morhua/ or Carps/ or Tuna/ or Perches/ or Esocidae/ or Anguilla/ or Fish products/	23484
4	("Trout?" or "Salmo trutta" or "Oncorhynchus mykiss" or "Salmo mykiss" or "Salmon?" or "salmo salar" or "Oncorhynchus" or "halibut?" or "flounder?" or "European plaice?" or "Hippoglossus hippoglossus" or "Pleuronectes platessa" or "platichthys flesus" or "Mackerel?" or "scomber scombrus" or "Haddock?" or "Melanogrammus aeglefinus" or "Saithe?" or "Pollachius virens" or "Cod?" or "Gadus Morhua" or "Codling?" or "Stockfish*" or "Clipfish*" or "Pollachius pollachius" or "Pollock?" or "Pollack?" or "Carp?" or "cyprinus carpio" or "merluccius merluccius" or "hake?" or "xiphias gladius" or "swordfish*" or "Tuna" or "Katsuwonus pelamis" or "Thunnus thynnus" or "Perch*" or "Perca fluviatilis" or "Perciform*" or "Clupea harengus" or "Herring?" or "Argentina silus" or "Salmo silus" or "Greater argentine" or "smelt?" or "Atlantic argentine" or "Wolffish*" or "Seawolf?" or "Anarhichadidae" or "anarhichas lupus" or "Esocidae" or "Esox lucius" or "Pike?" or "Lophius piscatorius" or "Anglerfish*" or "Monkfish*" or "Anguilla anguilla" or "Eel?" or "Conger conger" or "Sardina pilchardus" or "Sardine?" or "pilchard?" or "Anchov*" or "Engraulis encrasicolus" or "Sprattus	206110

	sprattus" or "European sprat" or "Brosme brosme" or "Merlangius merlangius" or "Whiting" or "fishproduct?").tw,kw.	
5	or/1-4	406916
6	Eating/ or exp Meals/ or Diet/	255553
7	("eat*" or "ate" or "intake?" or "consumption" or "consume?" or "consuming" or "ingestion" or "meal?" or "diet*" or "dine" or "dinner?" or "lunch*" or "breakfast?" or "snack?").tw,kw.	1466052
8	6 or 7	1504332
9	5 and 8	53701
10	Bone density/ or exp Bone Diseases, metabolic/ or exp Fractures, bone/ or Accidental Falls/	445799
11	("Osteoporosis" or "Rickets" or "Osteomalacia" or "vitamin D deficienc*" or (bone adj2 ("disease?" or "density" or "fracture?" or "fragil*" or "broken" or "deminerali#ation?" or "decalciferation?")) or "Accidental Fall*" or (("Slip?" or "trip?") adj2 "fall*")).tw,kw.	209908
12	exp Human development/ or Child Development/ or Motor disorders/ or Psychomotor Disorders/ or exp Psychomotor Performance/ or Cognition/ or Cognitive dysfunction/ or exp Neurocognitive disorders/ or Mental health/ or exp Academic performance/ or exp Child behavior/ or Impulsive Behavior/ or "Inhibition (Psychology)"/ or exp Language disorders/ or Mental disorders/ or Behavioral Symptoms/ or Behavior/ or Anxiety disorders/ or exp "Bipolar and related disorders"/ or Anger/ or Affect/ or Depression/ or Mood disorders/ or	3110493

	<p>Aggression/ or exp Schizophrenia/ or exp Neurodevelopmental Disorders/ or exp Autism spectrum disorder/ or Attention deficit disorder with hyperactivity/ or Attention/ or Learning/ or Reading/ or Mathematics/ or Aptitude tests/ or Language tests/ or Communication/ or Language/ or Language development/ or Child language/ or Literacy/ or Intelligence/ or Executive function/ or Social behavior/ or Social adjustment/ or Emotional intelligence/ or Emotions/ or Temperament/ or exp Amnesia/ or Memory Disorders/ or Dementia/ or Alzheimer disease/ or Memory, Short-Term/ or Memory, Long-term/</p>	
13	<p>((("Child*" or "infant*" or "f?etal" or "prenatal" or "pre natal" or "postnatal" or "post natal" or "human" or "antepartum period?" or "ante partum period?") adj3 "development?" or "inhibition" or ("brain" adj2 ("damage?" or "injur*" or "development?" or "disorder?")) or "psychomotor" or "psycho motor" or "motor" or "sensorimotor" or "sensori motor" or "sensorymotor" or "sensory motor" or "cognition" or "cognitive function?" or "Mental health" or "Disorder? of higher cerebral function?" or ("psychological" adj ("well being" or "wellbeing")) or (("neurocognit*" or "neuro cognit*" or "neurological" or "nervous system" or "nervoussystem" or "cognitive" or "development*" or "mental") adj2 ("dysfunction?" or "function?" or "decline?" or "deterioration?" or "Defici*" or "illness*" or "retardation?" or "disturbance?" or "impairment?" or "disorder?" or "impact?" or "disabilit*" or "deviation?" or "development?")) or "neurodevelopment*" or "neuro development*" or "autis*" or "asperger" or "kanner?" or "ASD" or "attention deficit" or "hyperactiv*" or "ADDH" or "ADHD" or "AD/HD" or "ADD" or "minimal brain dysfunction" or "impulsiveness" or "dyslexia" or "dyslexic?" or "dyscalculia" or "dyscalculic?" or "attention" or "learning" or "reading" or "mathematic?" or "math" or "maths" or ("aptitude" adj1 "test?") or ("Education" or "Educational" or "academic" or "school") adj1 ("Status" or "attainment?" or "achievement?" or "performance?" or "underachievement?" or "under achievement?" or "score?" or "success*" or "failure?")) or "executive function?" or "information processing" or "school readiness" or "school ready" or "Emotion*" or "socialemotional" or "social emotional" or "socioemotional" or "socio emotional" or ("social" adj ("development?" or "behavio?r" or "adjustment?")) or ("intel?ectual" adj2 ("development?" or "deficien*" or "disorder?" or "retardation?" or "disabilit*" or "disturbance?" or "impairment?")) or "Communication" or "language?" or</p>	7966130

	"literacy" or "literacies" or "IQ" or "intel?igence" or "Speech disorder?" or "mutism?" or "aphasia" or "stutter*" or "dysphasia" or "alexia" or "anxiet*" or "depression?" or "depressive" or "mood disorder?" or "schizophrenia" or "schizophrenic" or "aggression" or "behavio?r*" or "affect" or "anger" or "bipolar" or "Temperament?" or "personalit*" or "amnesia" or "dementia" or "Alzheimer?" or "Parkinson?" or "huntington?" or ("memory" adj3 ("disorder?" or "impairment?" or "disturbance?" or "deficianc*" or "disabilit*" or "short term" or "shortterm" or "long term" or "longterm" or "verbal recognition?"))).tw,kw.	
14	exp Cardiovascular diseases/ or Cerebrovascular disorders/ or exp Ischemia/ or exp Stroke/	3905261
15	((("Cardiovascular" or "heart" or "cardiac" or "myocardial" or "myo cardial" or "cerebrovascular" or "vascular" or "coronary" or "cerebral" or "peripheral" or "endothelial") adj ("disease?" or "disorder?" or "failure" or "event?" or "health" or "effect?" or "accident?" or "calcification?" or "risk factor?" or "riskfactor?" or "syndrom?" or "syndrome?" or "revasculari#ation?" or "arter*" or "function?" or "dysfunction?" or "attack?" or "arrest" or "apoplex*" or "insufficienc*" or "injur*" or "insult?" or "scleros#s" or "stenos#s" or "restenos#s")) or "cardioprotect*" or "cardio protect*" or "high cardiovascular risk?" or "CVD" or "infarct*" or "reinfarction?" or "aneurysm?" or "angina" or "atherosclero*" or "arthero sclero*" or "arteriosclero*" or "arterio sclero*" or "isch?emi*" or "nonisch?emi*" or "non isch?emic" or "thrombos#s" or "thrombolism?" or "tachycardia*" or "tachyarrhythmia?" or "arrhythmia?" or (("ventricular" or "arterial") adj ("fibrillation?" or "compliance?" or "stiffness*")) or "sudden cardiac death?" or "stroke?" or "TIA" or ("brain" adj ("h?emorrhage?" or "accident?" or "attack?" or "infarct*" or "insult?")))).tw,kw.	2440207
16	exp Dental Enamel/ or exp Dental Enamel Hypoplasia/ or Tooth Discoloration/	24761

17	((("dental" or "tooth" or "teeth" or "enamel") adj1 ("enamel" or "discolo?ration?" or "malformation?" or "opacit*")) or "hypo?minerali#ation" or ("developmental" adj3 ("dental" or "teeth" or "tooth" or "enamel") adj3 "defect?")).tw,kw.	28317
18	exp Immunity/ or Respiratory Sounds/ or exp Asthma/ or exp Psoriasis/ or exp Eczema/ or Dermatitis/ or exp Arthritis, Rheumatoid/ or Antibodies, antinuclear/ or exp Respiratory Tract Infections/ or exp Multiple sclerosis/ or Lupus Erythematosus, Systemic/ or Scleroderma, Localized/ or Scleroderma, Systemic/	2377093
19	("immunolog*" or "infection resistance" or "immunity" or "autoimmunity" or "auto immunity" or "immunodeficienc*" or "immuno deficienc*" or ("immun*" adj ("system" or "status" or "defense?" or "defence?" or "deficienc*")) or "vaccination response?" or (("upper" or "lower") adj "respiratory tract infection?") or "respiratory Sound?" or "wheez*" or "asthma*" or "psoriasis" or "eczema*" or "dermatiti*" or "rheumatoid arthritis" or (((("sjogren?" or "sicca") adj "syndrome?") or "syndrom?") or "Antinuclear antibod*" or "Multiple scleros#s" or "Systemic lupus erythematosus" or (("Scleroderma" or "scleros#s") adj1 ("localized" or "systemic")))).tw,kw.	2528520
20	Sperm count/ or Semen/ or exp Infertility, Male/ or exp Spermatozoa/ or Sexual maturation/ or Puberty/	129442
21	("Sperm?" or "semen" or "seminal fluid?" or "ejacul*" or "spermatozo*" or "spermatids" or "spermatocytes" or "spermatogonia" or "Oligospermia" or "Oligozoospermia*" or "Oligoasthenoteratozoospermia" or "asthenozoospermia?" or "asthenospermia?" or "criptozoospermia?" or "azoosperm*" or "globozoospermia?" or "teratospermia?" or "teratozoospermia?" or (("man" or "male?" or "men") adj1 "infertil*") or "Sex* matur*" or "Pubert*").tw,kw.	203032

22	Obesity/ or Abdominal obesity/ or Morbid obesity/ or Childhood obesity/ or Maternal obesity/ or Adolescent obesity/ or Body weight change/ or Body weight gain/ or Childhood obesity/ or Adipocyte/ or exp Body size/	510381
23	("obesity" or "obesities" or "obese" or "obesitas" or "adipos*" or "fat overload" or "overweight" or "over weight" or "BMI" or "body mass index" or "bodymass index" or "lean body mass" or "lean bodymass" or "fatness" or "adipocyte?" or "lipocyte?" or (("fat" or "lipid") adj cell?) or ("body" adj ("height?" or "size?" or "weight?")) or ("abdominal" adj ("diameter index" or "height")) or "sagittal abdominal diameter?" or "height weight ratio?" or "waist circumference?" or "waist height ratio?" or "waist to height ratio?" or ("weight" adj1 ("change*" or "gain*")) or ("excess*" adj2 ("fat" or "weight"))).tw,kw.	1105594
24	Birth weight/ or Pregnancy outcome/ or Premature birth/ or Growth/	189567
25	("growth" or (("premature" or "pre term" or "preterm") adj "birth?") or "SGA" or ("birth" or "gestational" or "neonatal" or "neo natal" or "newborn" or "new born" or "f?etal" or "f?etus" or "baby" or "babies") adj2 ("weight" or "size?")) or (("Pregnancy" or "birth" or "obstetric") adj "outcome?").tw,kw.	1763942
26	("allerg*" or "hypersensitivit*" or "hyper sensitivit*" or "sensiti#ation*" or "atopic?" or "atopy" or "atopies") adj5 "prevention").tw,kw.	4175
27	exp Diabetes mellitus/	915202
28	("diabetes" or "sugar sickness" or "hypoglycemia" or "hypo glycemia" or "hyperglycemia" or "hyper glycemia").tw,kw.	814988
29	exp Goiter/	22074

30	("goiter? " or "goitre? ").tw,kw.	20372
31	exp Mortality/	1025200
32	("mortalit*" or "death rate?" or "deathrate?").tw,kw.	1079973
33	or/10-32	17042583
34	9 and 33	31429
35	(animal/ or exp nonhuman/ or Animal experiment/) not ((animal/ or exp nonhuman/ or Animal experiment/) and exp human/)	5867700
36	34 not 35	19268
37	limit 36 to (conference abstracts or embase)	16382
38	limit 37 to (danish or english or french or german or norwegian or swedish)	15922

**Database:** PsycINFO

**Dato:** 26.11.2019

**Antall treff:** 1439

#	Searches	Results
1	Fishes/	7256
2	("Fishes" or "Fish").tw.	10342
3	Salmon/ or "Bass (fish)"/	247
4	("Trout?" or "Salmo trutta" or "Oncorhynchus mykiss" or "Salmo mykiss" or "Salmon?" or "salmo salar" or "Oncorhynchus" or "halibut?" or "flounder?" or "European plaice?" or "Hippoglossus hippoglossus" or "Pleuronectes platessa" or "platichtys flesus" or "Mackerel?" or "scomber scombrus" or "Haddock?" or "Melanogrammus aeglefinus" or "Saithe?" or "Pollachius virens" or "Cod?" or "Gadus Morhua" or "Codling?" or "Stockfish*" or "Clipfish*" or "Pollachius pollachius" or "Pollock?" or "Pollack?" or "Carp?" or "cyprinus carpio" or "merluccius merluccius" or "hake?" or "xiphias gladius" or "swordfish*" or "Tuna" or "Katsuwonus pelamis" or "Thunnus thynnus" or "Perch*" or "Perca fluviatilis" or "Perciform*" or "Clupea harengus" or "Herring?" or "Argentina silus" or "Salmo silus" or "Greater argentine" or "smelt?" or "Atlantic argentine" or "Wolffish*" or "Seawolf?" or "Anarhichadidae" or "anarhichas lupus" or "Esocidae" or "Esox lucius" or "Pike?" or "Lophius piscatorius" or "Anglerfish*" or "Monkfish*" or "Anguilla anguilla" or "Eel?" or "Conger conger" or "Sardina pilchardus" or "Sardine?" or "pilchard?" or "Anchov*" or "Engraulis encrasicolus" or "Sprattus sprattus" or "European sprat" or "Brosme brosmes" or "Merlangius merlangius" or "Whiting" or "fishproduct?").tw.	25620



5	or/1-4	37596
6	Food intake/ or Ingestion/ or Diets/ or Food intake/	28654
7	("eat*" or "ate" or "intake?" or "consumption" or "consume?" or "consuming" or "ingestion" or "meal?" or "diet*" or "dine" or "dinner?" or "lunch*" or "breakfast?" or "snack?").tw.	218666
8	6 or 7	220834
9	5 and 8	2766
10	Osteoporosis/ or exp Bone disorder/ or Falls/	4134
11	("Osteoporosis" or "Rickets" or "Osteomalacia" or "vitamin D deficienc*" or (bone adj2 ("disease?" or "density" or "fracture?" or "fragil*" or "broken" or "deminerali#ation?" or "decalciferation?")) or "Accidental Fall*" or (("Slip?" or "trip?") adj2 "fall*")).tw.	3869
12	exp Human development/ or exp Childhood development/ or exp Prenatal development/ or Postnatal development/ or Nervous system disorders/ or Psychomotor development/ or Motor development/ or Cognition/ or Cognitive impairment/ or Cognitive development/ or exp Neurocognitive disorders/ or Mental health/ or exp Academic achievement/ or Child behavior/ or Behavior problems/ or Impulsiveness/ or "Inhibition (personality)"/ or exp Language disorders/ or Mental disorders/ or Behavior/ or Anxiety disorders/ or exp Bipolar disorder/ or Anger/ or Affection/ or "Depression (Emotion)"/ or Affective disorders/ or Aggressiveness/ or exp Schizophrenia/ or exp Neurodevelopmental Disorders/ or Attention/ or Learning/ or Reading/ or Mathematics/ or Aptitude Measures/ or Communication/ or Language/ or Language development/ or	1222907

	<p>Literacy/ or Intelligence/ or Executive function/ or Social behavior/ or Social adjustment/ or Emotional intelligence/ or Emotions/ or Personality/ or exp Amnesia/ or Memory Disorders/ or Dementia/ or "Alzheimer's disease"/ or Short term memory/ or Long term memory/</p>	
13	<p>((("Child*" or "infant*" or "f?etal" or "prenatal" or "pre natal" or "postnatal" or "post natal" or "human" or "antepartum period?" or "ante partum period?") adj3 "development?" or "inhibition" or ("brain" adj2 ("damage?" or "injur*" or "development?" or "disorder?")) or "psychomotor" or "psycho motor" or "motor" or "sensorimotor" or "sensori motor" or "sensorymotor" or "sensory motor" or "cognition" or "cognitive function?" or "Mental health" or "Disorder? of higher cerebral function?" or ("psychological" adj ("well being" or "wellbeing")) or (("neurocognit*" or "neuro cognit*" or "neurological" or "nervous system" or "nervoussystem" or "cognitive" or "development*" or "mental") adj2 ("dysfunction?" or "function?" or "decline?" or "deterioration?" or "Defici*" or "illness*" or "retardation?" or "disturbance?" or "impairment?" or "disorder?" or "impact?" or "disabilit*" or "deviation?" or "development?")) or "neurodevelopment*" or "neuro development*" or "autis*" or "asperger" or "kanner?" or "ASD" or "attention deficit" or "hyperactiv*" or "ADDH" or "ADHD" or "AD/HD" or "ADD" or "minimal brain dysfunction" or "impulsiveness" or "dyslexia" or "dyslexic?" or "dyscalculia" or "dyscalculic?" or "attention" or "learning" or "reading" or "mathematic?" or "math" or "maths" or ("aptitude" adj1 "test?") or (("Education" or "Educational" or "academic" or "school") adj1 ("Status" or "attainment?" or "achievement?" or "performance?" or "underachievement?" or "under achievement?" or "score?" or "success*" or "failure?")) or "executive function?" or "information processing" or "school readiness" or "school ready" or "Emotion*" or "socialemotional" or "social emotional" or "socioemotional" or "socio emotional" or ("social" adj ("development?" or "behavio?r" or "adjustment?")) or ("intel?ectual" adj2 ("development?" or "deficien*" or "disorder?" or "retardation?" or "disabilit*" or "disturbance?" or "impairment?")) or "Communication" or "language?" or "literacy" or "literacies" or "IQ" or "intel?igence" or "Speech disorder?" or "mutism?" or "aphasia" or "stutter*" or "dysphasia" or "alexia" or "anxiet*" or "depression?" or "depressive" or "mood disorder?" or "schizophrenia" or "schizophrenic" or "aggression" or "behavio?r*" or "affect" or "anger" or</p>	3088911

	"bipolar" or "Temperament?" or "personalit*" or "amnesia" or "dementia" or "Alzheimer?" or "Parkinson?" or "huntington?" or ("memory" adj3 ("disorder?" or "impairment?" or "disturbance?" or "deficianc*" or "disabilit*" or "short term" or "shortterm" or "long term" or "longterm" or "verbal recognition?"))).tw.	
14	exp Cardiovascular disorders/ or Cerebrovascular disorders/ or Cerebrovascular accident/	60364
15	((("Cardiovascular" or "heart" or "cardiac" or "myocardial" or "myo cardiac" or "cerebrovascular" or "vascular" or "coronary" or "cerebral" or "peripheral" or "endothelial") adj ("disease?" or "disorder?" or "failure" or "event?" or "health" or "effect?" or "accident?" or "calcification?" or "risk factor?" or "riskfactor?" or "syndrom?" or "syndrome?" or "revasculari#ation?" or "arter*" or "function?" or "dysfunction?" or "attack?" or "arrest" or "apoplex*" or "insufficienc*" or "injur#" or "insult?" or "scleros#" or "stenos#" or "restenos#s")) or "cardioprotect*" or "cardio protect*" or "high cardiovascular risk?" or "CVD" or "infarct*" or "reinfarction?" or "aneurysm?" or "angina" or "artherosclero*" or "arthero sclero*" or "arteriosclero*" or "arterio sclero*" or "isch?emi*" or "nonisch?emi*" or "non isch?emic" or "thrombos#" or "thrombolism?" or "tachycardia*" or "tachyarrhythmia?" or "arrhythmia?" or (("ventricular" or "arterial") adj ("fibrillation?" or "compliance?" or "stiffness*")) or "sudden cardiac death?" or "stroke?" or "TIA" or ("brain" adj ("h?emorrhage?" or "accident?" or "attack?" or "infarct*" or "insult?"))).tw.	91719
16	((("dental" or "tooth" or "teeth" or "enamel") adj1 ("enamel" or "discolo?ration?" or "malformation?" or "opacit*")) or "hypo?minerali#ation" or ("developmental" adj3 ("dental" or "teeth" or "tooth" or "enamel") adj3 "defect?"))).tw.	77
17	exp Respiratory tract disorders/ or Eczema/ or exp Dermatitis/ or Rheumatoid arthritis/ or Asthma/	16589

18	("immunolog*" or "infection resistance" or "immunity" or "autoimmunity" or "auto immunity" or "immunodeficienc*" or "immuno deficienc*" or ("immun*" adj ("system" or "status" or "defense?" or "defence?" or "deficienc*")) or "vaccination response?" or (("upper" or "lower") adj "respiratory tract infection?" or "respiratory Sound?" or "wheez*" or "asthma*" or "psoriasis" or "eczema*" or "dermatiti*" or "rheumatoid arthritis" or (((("sjogren?" or "sicca") adj "syndrome?" or "syndrom?") or "Antinuclear antibod*" or "Multiple scleros#s" or "Systemic lupus erythematosus" or (("Scleroderma" or "scleros#s") adj1 ("localized" or "systemic")))).tw.	139603
19	Sperm/ or Psychosexual development/ or Puberty/	6415
20	("Sperm?" or "semen" or "seminal fluid?" or "ejacul*" or "spermatozo*" or "spermatids" or "spermatocytes" or "spermatogonia" or "Oligospermia" or "Oligozoospermia*" or "Oligoasthenoteratozoospermia" or "asthenozoospermia?" or "asthenospermia?" or "criptozoospermia?" or "azoosperm*" or "globozoospermia?" or "teratospermia?" or "teratozoospermia?" or (("man" or "male?" or "men") adj1 "infertil*") or "Sex* matur*" or "Pubert*").tw.	14887
21	Overweight/ or Obesity/ or Adipocytes/ or Body Mass Index/ or Weight gain/ or exp Body size/	57278
22	("obesity" or "obesities" or "obese" or "obesitas" or "adipos*" or "fat overload" or "overweight" or "over weight" or "BMI" or "body mass index" or "bodymass index" or "lean body mass" or "lean bodymass" or "fatness" or "adipocyte?" or "lipocyte?" or (("fat" or "lipid") adj cell?) or ("body" adj ("height?" or "size?" or "weight?")) or ("abdominal" adj ("diameter index" or "height")) or "sagit?al abdominal diameter?" or "height weight ratio?" or "waist circumference?" or "waist height ratio?" or "waist to height ratio?" or ("weight" adj1 ("change*" or "gain*")) or ("excess*" adj2 ("fat" or "weight")))).tw.	79105

23	Birth weight/ or Pregnancy outcomes/ or Premature Birth/ or Development/	15445
24	("growth" or (("premature" or "pre term" or "preterm") adj "birth?") or "SGA" or (("birth" or "gestational" or "neonatal" or "neo natal" or "newborn" or "new born" or "f?etal" or "f?etus" or "baby" or "babies") adj2 ("weight" or "size?")) or (("Pregnancy" or "birth" or "obstetric") adj "outcome?")).tw.	106935
25	((("allerg*" or "hypersensitivit*" or "hyper sensitivit*" or "sensiti#ation*" or "atopic?" or "atopyor atopies") adj5 "prevention")).tw.	42
26	exp Diabetes mellitus/	8074
27	("diabetes" or "sugar sickness" or "hypoglycemia" or "hypo glycemia" or "hyperglycemia" or "hyper glycemia").tw.	30009
28	exp Goiters/	44
29	("goiter? " or "goitre? ").tw.	226
30	"Death and Dying"/	29933
31	("mortalit*" or "death rate?" or "deathrate?").tw.	40312
32	or/10-31	3351801
33	9 and 32	2225

34	(animal not (animal and human)).po.	355388
35	33 not 34	1489
36	limit 35 to (danish or english or french or german or norwegian or swedish)	1439

# Appendix III

## Compounds that will be considered for inclusion in the RBA

Group	Compound name
Brominated flame retardants	$\Sigma$ PBDEs, including DecaBDE
Brominated flame retardants	1,2-Bis(2,4,6-tribromophenoxy)ethane
Brominated flame retardants	DBDE (feil navn? Sjekk med Gro!). DBPDE ( <a href="https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2012.2908">https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2012.2908</a> )
Brominated flame retardants	HBB
Brominated flame retardants	HBCDD
Brominated flame retardants	2,4,6-Tribromophenol (TBP)
Pesticides	Chlorpyrifos
Pesticides	Phosphoric acid-phosphates
Pesticides	HCB
Pesticides	HCH
Pesticides	<i>trans</i> -Nonachlor
Pesticides	DDT
Pesticides	DDE

Mycotoxins	Aflatoxin
Mycotoxins	Beauvericin
Mycotoxins	Enniatin B
Perfluorinated compounds	PFOS
Perfluorinated compounds	PFOA
Perfluorinated compounds	PFHxS
Perfluorinated compounds	PFNA
Perfluorinated compounds	PFDA
Perfluorinated compounds	PFUnDA
Perfluorinated compounds	PFHpS
Dioxins and dl-PCBs; group of compounds	
non-dioxin-like PCBs; group of compounds	$\Sigma$ PCB6
non-dioxin-like PCBs; group of compounds	PCB153
non-dioxin-like PCBs; group of compounds	PCB138
Phthalates; group of compounds	
Glycidyl fatty acid esters (GEs)	Glycidyl fatty acid esters (GEs)
MeHg	MeHg
Antioxidants	BHT (butylhydroxytoluene)
Antioxidants	Ethoxyquin (EQ)



Erucic acid	Erucic acid
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Total arsenic	Total arsenic
Inorganic arsenic	Inorganic arsenic
Organic arsenic	Organic arsenic
Siloxanes	Siloxan D4
Siloxanes	Siloxan D5
Siloxanes	Siloxan D6
Bisphenols	Bisphenol A
Bisphenols	Bisphenol G
Bisphenols	Bisphenol TMC
Bisphenols	Bisphenol F